2. (amended) The method of Claim 1 wherein said condition is the result of neurodegenerative disease.

9. (amended) The method of Claim 1 wherein said EPO is a recombinant form thereof.

REMARKS

Claims 1 to 10 were pending in the instant application. By this amendment, Claims 7 and 10 have been canceled, without prejudice to pursue the subject matter of the cancelled claims in another application, and Claims 1, 2 and 9 have been amended, to comply with the Examiner's restriction requirement and requirement for species election. In addition, Claim 1, and claims dependent thereon, has been amended to specify the peripheral administration of an effective *non-toxic* amount of erythropoietin. This amendment is fully supported by the specification and claims as originally filed (*e.g.*, see Summary of the Invention at p.4, *ll.* 26-27). As such, no new matter has been introduced by this amendment.

The specification has been amended to change the title of the invention to more accurately reflect the claimed subject matter, to include a specific reference to the priority applications in the first sentence of the specification, and to correct a typographical error in the Brief Description of the Figures. Applicants assert that the amendments to the specification do not introduce new matter.

Therefore, Claims 1-6, 8, and 9 will be pending upon entry of the instant amendment. Entry of the amendments and the remarks made herein into the record for the above-identified application is respectfully requested.

1. THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claim 1 is rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In response, Claim 1 has been amended to overcome the Examiner's rejection for lack of antecedent basis for "said mammal." As such, applicants request withdrawal of the rejection for indefiniteness under 35 U.S.C. § 112, second paragraph.

2. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1-6, 8 and 9 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants respectfully submit that the rejections have been overcome and/or obviated in veiw of the above-made amendments and for the reasons discussed below.

First, the Examiner contends that the specification fails to provide an enabling disclosure of a method for treatment or prevention of a neurodegenerative condition. In particular, the Examiner contends that the specification does not teach how to prevent the onset of a neurodegenerative condition.

Applicants submit that methods for prevention and treatment are fully enabled by the instant application. As evidence that the described methods of treatment are enabled by the application as filed, applicants direct the Examiner's attention to the Declaration of Michael L. Brines, M.D , Ph.D. ("the Brines Declaration"), which is attached hereto as Exhibit F. Briefly, the Brines Declaration presents the results of successful experiments that demonstrate efficacy of EPO treatment in protection against neurodegenerative conditions in two art-recognized models of human neurodegenerative conditions, the rat experimental neuropathy model and the mouse SOD model. The results of experiments carried out with both model systems demonstrate that EPO treatment, administered in accordance with the methods disclosed in the application as originally filed, provides a protective benefit for a number of neuropathological symptoms and conditions found in these animal models. In particular, the experiments descriibed in the Brines Declaration show that EPO protects against neurodegeneration and loss of muscle coordination function in both the rat (see Brines Declaration, ¶¶ 8-12 and Appendices 3-4) and mice (see Brines Declaration, ¶15-16 and Appendix 5) model systems.

Second, the Examiner contends that the specification is not enabled for the treatment or prevention of the broad class of neurodegeneration conditions, because neurodegenerative diseases are a varied assortment of central nervous tissue disorders characterized by gradual and progressive loss of neural tissue. While applicants agree with the Examiner that neurodegenerative diseases are a varied assortment of disorders, applicants submit that common mechanisms underlie many of these various neurodegenerative disorders. Indeed,

oxidative stress resulting from free radical mechanisms causes the neuronal cell death and progression of neuropathology, the primary cause of many such neurodegenerative diseases (*see* Brines Declaration, ¶ 17, and references cited therein). According to the instantly claimed methods, EPO can be used to protect neural tissue from damage resulting from such hypoxic conditions, and thereby prevent and protect against a such broad assortment of neurodegenerative conditions and diseases (see specification, p. 4, *ll.*11-13, and p.11, lines 25-26).

The Examiner further contends that the claims are only enabled for EPO amounts that do not increase hemoglobin concentration or hematocrit. The Examiner argues that, because increases in hemoglobin or hematocrit have been shown to cause detrimental effects in patients, severe complications, such as hypertension, strokes or seizures can occur in patients receiving high doses of EPO over longer periods of time versus a bolus injection of EPO.

In response, Claim 1 has been amended to recite a "non-toxic" amount of EPO. Applicants assert that the claims are fully enabled by the specification, not only for EPO amounts that do not increase hemoglobin concentration or hematocrit, but also for the claimed non-toxic amounts of EPO. The specification describes formulations and non-toxic dosages of erythropoietin that could be used to achieve neuroprotection (specification at p. 22, *l.* 25 to p. 24, *l.* 6; see also p.4, *ll.* 26-27). Applicants submit that the claimed method is fully described and enabled by the teachings of the specification as it would be understood and applied by one skilled in the art. The instant specification also enumerates the factors that should be considered to determine appropriate <u>non-toxic</u> dosage of erythropoietin, and specifies that the skilled practitioner should readily be able to make such a determination according to standard clinical techniques. For example, p. 22, *l.* 32 to p. 23, *l.* 9 states:

> Selection of the preferred effective dose will be determined by a skilled artisan based upon considering several factors which will be known to one of ordinary skill in the art. Such factors include the particular form of erythropoietin, and its pharmacokinetic parameters such as bioavailability, metabolism, half-life, etc., which will have been established during the usual development procedures typically employed in obtaining regulatory approval for a pharmaceutical compound further factors in considering the dose include the condition or disease to be treated or the benefit to be achieved in a normal individual, the body mass of the patient, the route of administration, whether administration is acute or chronic, concomitant medications, and other factors well known to

> affect the efficacy of administered pharmaceutical agents. Thus the precise dosage should be decided according to the judgment of the practitioner and each patient's circumstances, *e.g.*, depending upon the condition and the immune status of the individual patient, according to standard clinical techniques.

Given this direction, the skilled practitioner would be able to make appropriate determinations and choices using ordinary skill. In this regard, the Examiner's attention is invited to the 2000 edition of the Physicians' Desk Reference ("PDR"), the art-accepted standard reference manual for practitioners at the relevant time; and, in particular, the section of the PDR relating to erythropoietin (see PDR, pp. 519-525 and 2125-2131, a copy of which is provided herewith as Exhibit E). The PDR shows that, depending on the patient population being treated with erythropoietin, different hematocrit ranges are targeted to avoid toxicity.[1] The PDR shows that practitioners monitor the patient's hematocrit during therapy with erythropoietin and, to avoid toxicity, adjust the dose and/or withhold treatment if the patient's hematocrit approaches or exceeds the upper limits of a target range. Therefore, the skilled practitioner, armed with the teachings of the instant specification, would be able to administer doses of erythropoietin sufficient to achieve neuroprotective effects, yet avoid toxic side effects, *e.g.*, simply by monitoring the patient's hematocrit and adjusting the dosing of erythropoietin to maintain the patient's hematocrit within the desired target range. Thus, the teachings of the instant application can be successfully practiced without undue experimentation, and the claims are enabled.

In view of the foregoing, applicants submit that the rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, is in error and should be withdrawn.

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[1] For example, in patients with chronic renal failure, the PDR recommends dosing erythropoietin to achieve non-toxic target hematocrits ranging from 30% to 36% (*e.g.*, see PDR, p. 523, col. 1, *ll.* 17-96 and p. 2129, col. 1, *ll.* 8-93, and accompanying table in cols. 2 and 3). The PDR notes that toxicity in the form of polycythemia (a condition marked by an abnormal increase in the number of circulating red blood cells) can be avoided by carefully monitoring the hematocrit and adjusting doses of EPO, withholding erythropoietin if the hematocrit approaches the high-end of the target range (36% for this patient population) or increases by more than 4 points in any 2-week period, until the hematocrit returns to the suggested target range (30% to 36% for this patient population; see PDR, p. 523, col. 1, and p. 2129, col. 1, under "Dose Adjustment"). In contrast, for cancer patients on chemotherapy, the PDR teaches to adjust the dosage at a different hematocrit level, *i.e.*, if the hematocrit exceeds 40% (see p. 2129, col. 2, under "Dose Adjustment").

3. MISCELLANEOUS MATTERS

Applicants take this opportunity to bring to the attention of the Examiner the reference Albayrak *et al.*, 1997, ACTA Neuropathol. 94: 158-163 ("Albayrak"), a copy of which is provided herewith as Exhibit D. Applicants believe Albayrak supports the patentability of the instantly claimed invention, and is merely cumulative to information already of record in the instant application, and therefore is not material to patentability under Rule 1.56(b). Although Albayrak has not been cited in connection with any of the applicants' counterpart foreign applications, we take this opportunity to note that Albayrak was cited by the European Patent Office in connection with the European examination of WO 00/35475 (Ref. AR of record). Applicants note that reference AR designates the United States, and according to the USPTO records, entered the national stage on June 28, 2001 as U.S. Application No. 09/868,089.

CONCLUSIONS

Applicants respectfully request that the foregoing amendments and remarks be made of record in the file history of the instant application. Applicants estimate that the remarks and amendments made herein now place the pending claims in condition for allowance.

Respectfully submitted,

Date: February 26, 2003

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Enclosures

EXHIBIT A:
MARKED-UP VERSION OF THE AMENDMENTS TO THE SPECIFICATION
[additions shown by underlining and deletions shown by strikeouts]

On pages i and 1, please amend the title as follows:

[MODULATION OF EXCITABLE TISSUE FUNCTION] METHODS FOR PREVENTION AND TREATMENT OF NEURODEGENERATIVE CONDITIONS BY PERIPHERALLY ADMINISTERED ERYTHROPOIETIN

On page 1, replace the first paragraph with the following paragraph:

This application claims priority under 35 U.S.C. §119(e) to U.S. provisional patent Application No. 60/129,131 filed April 13, 1999 and under 35 U.S.C. §120 to U.S. Application No. 09/547,220 filed April 11, 2000, the entire contents of both of which ~~is~~ are incorporated herein by reference in ~~its~~ their entirety.

On p.7, replace the second paragraph with the following paragraph:

[FIG. 3A-B.] FIG. 3A-C. **A.** The results of an experiment which demonstrates that peripherally-administered EPO pretreatment reduces seizure severity and protects mice from convulsions and death by the neurotoxin kainate. The numbers in parentheses under each column indicate the number of animals receiving each kainate dose. **B** shows that the protective effects of peripherally-administered EPO increase with daily administration of EPO. **C** illustrates that the onset of action of EPO is delayed, characteristic of the induction of a gene expression program.

EXHIBIT B:
MARKED-UP VERSION OF THE CLAIM AMENDMENTS
(with additions shown by underlining and deletions shown within brackets)

1. (amended) A method for the prevention or treatment of a neurodegenerative condition comprising administering peripherally to [said] a mammal an effective non-toxic amount of EPO[, an EPO receptor activity modulator, or an EPO-activated receptor modulator, for the protection of an excitable tissue].

2. (amended) The method of Claim 1 wherein said condition is the result of [age-related loss of cognitive function, cerebral palsy,] neurodegenerative disease[, Alzheimer's disease, Parkinson's disease, Leigh disease, AIDS dementia, memory loss, multiple sclerosis, amyotrophic lateral sclerosis, alcoholism, mood disorder, anxiety disorder, attention deficit disorder, autism, Creutzfeld-Jakob disease, brain or spinal cord trauma, glaucoma, retinal ischemia, or retinal trauma].

9. (amended) The method of Claim 1 wherein said EPO is [erythropoietin, an erythropoietin analog, an erythropoietin mimetic, an erythropoietin fragment, a hybrid erythropoietin molecule, an erythropoietin receptor-binding molecule, an erythropoietin agonist, a renal erythropoietin, a brain erythropoietin, an oligomer thereof, a multimer thereof, a mutein thereof, a congener thereof, a naturally-occurring form thereof, a synthetic form thereof,] a recombinant form thereof[, or a combination thereof].